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THE CHICAGO MEDICAL SCHOOL QUARTERLY

VOLUME 17, NUMBER 4 AUGUST, 1956

CONTENTS

ERRATA

Several errors appeared in the May, 1956 issue of the QUARTERLY and should be corrected as follows:

1. Page 131 — Caption to Fig. 1 should read: **"Atypical** parenchymal regeneration . . ."

2. Page 132 — Caption to Fig. 2 should read: "Liver. Portal Cirrhosis. Bile canaliculi containing 'bile thrombi.' H. E. 680X."

3. Page 133 — Caption to Fig. 3 should read: "Same as figure 1. High magnification of the necrotic parenchymal cells. H. E. 720X."

4. Page 134 — The last line in column should be omitted. The last sentence of Dr. Kirchen's discussion should read as follows: "These facts should be kept in mind whenever a jaundiced patient is given antibiotics that can sterilize the gastrointestinal tract."

5. Page 136 — Caption to Fig. 8 should read: **"Cholemic** nephrosis."

6. Page 137 — The first paragraph in column 1 should read as follows: "Lack of increased urobilinogen secretion in the presence of such severe liver cell destruction may also be explained by the presence of an obstructive mechanism superimposed upon hepato-cellular damage."

THE CHICAGO MEDICAL SCHOOL
QUARTERLY

VOLUME 17 AUGUST 1956 NUMBER 4

DERIVATIVES OF SULFONYLUREA WITH HYPOGLYCEMIC ACTION[1]

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I. Introduction

The medical literature contains countless reports of orally effective hypoglycemic substances, reflecting a long history of hopes and disappointments in the endless search for an oral insulin substitute. Among the many substances which have achieved a certain, albeit fleeting, degree of popularity are yeast, thiamine and cocarboxylase, vitamin E, cobalt chloride, guanidine and its derivative synthalin A, and even the toxin of the poisonous mushroom Amanita phalloides. Most of these drugs have been abandoned because they are ineffective or exceedingly toxic to liver, kidney and other tissues, including, sometimes, the A cells of the islets of Langerhans. With the discovery of glucagon and the suggestion that its overproduction may play a role in the pathogenesis of diabetes mellitus, injury to the A cells became a plausible explanation for the hypoglycemic effects of these substances. As a result of this hypothesis, numerous attempts to treat human and experimental diabetes by means of selective destruction of the A cells have been made, generally without success. The weakness of this hypothesis and the disadvantages of some of the drugs have been discussed elsewhere[1-5]. In 1942 Janbon and collaborators[6] accidentally discovered the hypoglycemic effects of para-aminobenzene-sulfamido-isopropyl-thiodiazol (2254-RP, VK-57, or IPTD), while screening several compounds for their therapeutic value in typhoid fever. Loubatieres[7] immediately understood the importance of this observation, but interest in the problem did not become widespread until after the publication of experimental and clinical results obtained with another compound 1-butyl-3-sulfanyl-urea (BZ-55 or Carbutamide[8-10]). Soon other substances with hypoglycemic activity were described, including plant growth regulators[11, 12], derivatives of methylcholine[13] and other derivatives of sulfonylurea.

II. Chemistry

Among the sulfonylureas, IPTD was the first one to be studied and modified in an attempt to find more potent compounds and to correlate chemical structure with biological activity[6, 7]. Thus butyl, isobutyl and amyl derivatives were found to have greater hypoglycemic activity than the isopropyl derivative[14], while the cyclopropyl[15] and other derivatives[16] were also found active. In this paper, the discussion will be limited to the following three compounds which have been more extensively investigated from the experimental and clinical standpoint and, unless stated otherwise, it will refer collectively to all three.

[1] Aided by grant A-522 from the National Institute of Arthritis and Metabolic Diseases, N. I. H., Public Health Service..

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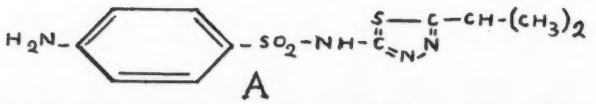
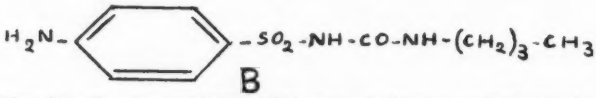


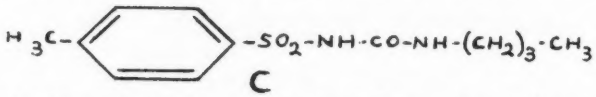
A

2-(para-aminobenzene-sulfamido)-5-isopropyl-thiodiazol, 2254-RP, VK-57, PASIT or IPTD.



B

1-butyl-3-sulfonyl-urea, U-6987, BZ-55, Invenol, Nadisan or Carbutamide.



C

1-butyl-3-p-tolyl-sulfonyl-urea, U-2043, D-860, Rastinon, Artosin, Orinase or Tolbutamide.

III. Pharmacology

A) *Absorption, Fate Excretion.* The sulfonylureas cause hypoglycemia in mice, rats, guinea pigs, rabbits, dogs and in man when given subcutaneously, intramuscularly, intraperitoneally, intravenously and orally. Gastro-intestinal absorption is rapid[8], especially if the drugs are administered in an alkaline medium[17]. Fecal elimination is very low, amounting to only 5-8% of the administered dose[18]. This allows the appearance in the plasma of measurable amounts of drug within 30 minutes and of effective concentrations (about 10 mg/100cc), within 3 to 6 hours after the administration of a single dose[19]. A large proportion of the drug circulates protein-bound[18], a fact which contributes to its very low disappearance[19, 20], even after intravenous injection[9]. The maintenance of effective plasma concentrations is aided also by the ability of the renal tubule to reabsorb 90 to 95% of the filtered drug, resulting in a plasma clearance of only 1 to 5 cc/min.[18]. Eventually, however, urinary excretion accounts for more than 90% of the administered dose, but this requires several days[21]. A large fraction of the absorbed carbutamide is acetylated[18, 19], while tolbutamide is oxidized to its carboxylic acid derivative[22, 23]. The organ distribution of the drugs is similar to that of sulfanylamide and the drugs have no tendency to concentrate in any given organ, including liver and pancreas[17, 18, 24].

B) *Dosage, Acute and Chronic Toxicity.*. The ideal dosage for the 3 drugs has not been established with certainty as yet and varies from patient to patient. Loubatieres and collaborators[25] recommend the following schedule for IPTD: 8-10 g/day for 1 to 3 days; gradual decrease to 3g/day during the following 4 to 20 days; maintenance dose of 2 to 3g/ day until the results have been stabilized; reduction of the maintenance dose to 1-1.5g/day for an unlimited time. Using para-aminobenzene-sulfamido-tertiobutyl-thiodiazol, the dosage could be reduced to the following: 2-3g on the first day, 2g on the second day, followed by a maintenance dose of 0.5-1g/day[26]. Satisfactory blood levels can be obtained with similar doses of carbutamide or tolbutamide corresponding to approximately 50mg/Kg/day and varying somewhat from clinic to clinic[A, 19, 21]. Larger doses do not appear to give better results[19, 27]. Drug responsiveness can be studied measuring the patient's blood sugar 4 hours after an oral test dose of 2-3g or an intravenous test dose of 1g: a decrease of 20% or more indicates individuals most likely to respond to treatment[27-30]. Insulin should be discontinued for 24 hours before the test and its dose carefully readjusted during treatment to avoid excessive hypoglycemia[31]. Acute hypoglycemia can be obtained in rabbits and dogs with intravenous doses of 50 to 250 mg/Kg[9, 32, 33]. A chronic state of

hypoglycemia can be maintained by feeding a diet containing about 0.5% of the drug to mice, rats, rabbits, cats and dogs[17, 20, 32]. Larger doses cause more profound and prolonged hypoglycemia from which the animal may not recover unless treated with glusose or glucagon[32]. The intravenous LD_{50} of carbutamide in mice is 1.9 g/Kg, the oral LD_{50} is 3.5 g/Kg[32]. The corresponding doses of tolbutamide are 0.6 and 2.5 g/Kg, respectively[17]. Death is accompanied by convulsions with hyperglycemia, and cannot be prevented by the injection of glucose, although cortisone seems to afford some degree of protection[14]. Chronic toxicity studies indicate that rats tolerate well diets containing 0.25 or 0.5% carbutamide for as long as 5 months[32]. Tolbutamide can be fed to rats in doses of 0.5 and 1.0 g/Kg for as long as 4 weeks without clinical and histological evidence of undesirable effects; dogs tolerate doses of 100 mg/Kg equally well, while higher doses (1-2 g/Kg) may cause focal lesions in the renal tubules of rabbits[35]. Crystalluria occurs only rarely in rats fed similarly high doses[36] but not in animals and men receiving therapeutic doses. This is due probably to the relatively high solubility of the drugs at the usual range of urinary pH. For example, the solubility of tolbutamide at pH 6 is significantly greater, and at pH 7, eight times greater than that of sulfamethazine, the most soluble of the "triple sulfas"[36]. "Albuminuria" has been reported in some cases, however since the carboxylic acid derivative of tolbutamide found in the urine precipitates with picric and sulfosalicyclic acid, the use of these albumin reagents may have caused false positive reactions in patients receiving the drug[22]. A slight hypertrophy of the thyroid was observed in rats receiving large doses of sulfonylureas[20, 32]. Effects on liver, pancreas and adrenals will be discussed below. The toxicity of sulfonylureas in diabetic patients receiving therapeutic doses is comparable to that of the sulfonamides. In a series of about 7000 patients treated with carbutamide, severe hematologic, hepatic and generalized reactions occurred in about 2% of the cases. Milder skin and gastro-intestinal reactions in an additional 3%. In other series of 279 and 193 cases respectively, treated with carbutamide the incidence of toxicity was 9%[37, 38]. Among the observed untoward reactions are: nausea, vomiting and diarrhea, skin eruptions and pruritus, leucopenia, granulocytopenia, and trombocytopenia, slight decrease in I^{131} uptake and PBI and mild thyroid hypertrophy, and febrile reactions[19, 25, 31, 38-43]. Damage to the liver and jaundice are extremely rare but may occur in some cases, especially in patients already suffering from liver disease[44, 45]. In most cases all signs of toxicity disappear upon interruption of treatment, although several deaths have occurred in patients receiving sulfonylureas[37, 38] and may or may not have been a direct effect of the drug. Hypoglycemic reactions are rare and respond promptly to treatment. No striking differences between the toxicity of carbutamide and that of tolbutamide have been reported, although according to some reports, tolbutamide may be slightly less toxic[46, 47, 48]. A definite conclusion on this important point cannot be reached as yet due to the fact that many more patients have been treated with carbutamide, than with tolbutamide[A].

C. *Mechanisms of Action.* Sulfonylurea hypoglycemia may be explained in a number of different ways, such as: 1) *Destruction of the A cells of the islets of Langerhans and decreased formation of glucagon.* Damage to the A cells was noted in experimental animals treated with a variety of hypoglycemic agents, such as $CoCl_2$, synthalin A, amanita toxin, IPTD and in 1 patient treated with carbutamide[8, 49-51]. However, hypoglycemia may occur in normal animals and in diabetic patients without A cell damage[52-55] or with only some degranulation or vacuolization[53, 57] and this hypothesis does not appear adequate to explain all observed facts. Furthermore, the hypothesis requires acceptance of the following premises: a) that the A cells are the site of action of glucagon which is probable, but not certain, and b) that glucagon plays a role in diabetes mellitus which is possible, but improbable[1-3]. 2) *Inhibition of liver glycogenolysis.* Liver glycogenolysis occurs in three steps:

1. Glycogen + inorganic phosphate ⇄ glucose-1-phosphate

2. glucose-1-phosphate ⇄ glucose-6-phosphate

3. glucose-6-phosphate ⇄ glucose + inorganic phosphate

These reactions are catalyzed by the enzymes phosphorylase, phosphoglucomutase and glucose-6-phosphatase, respectively. A slowdown in any one of them could result in an accumulation of liver glycogen and hypoglycemia. Treatment with sulfonylureas causes an increase in liver glycogen[16, 20, 24], especially during fast when glycogenolysis is usually at its peak[21, 51]. Depression of liver glucose output and of the glycogenolytic effects of glucagon and epinephrine by carbutamide and tolbutamide *in vivo* and *in vitro* have been described[35, 58-61], suggesting that the drugs may inhibit phosphorylase. However, other investigators[8, 58, 62, 63-64] could not confirm these results, except with concentrations of drug greater than the plasma levels required to obtain hypoglycemia in the intact animal. In addition phosphorylase is inhibited also by gantrisin which has no hypoglycemic effect[65]. The effect of sulfonylureas on the second glycogenolytic reaction catalized by phosphoglucomutase has not been investigated, while glucose-6-phosphatase activity and the third glycogenolytic reaction are depressed only moderately[51, 66], and at a time which does not coincide with the fall in blood sugar[67] or not at all[68]. There is some indication that the sulfonylureas may inhibit other liver enzymes such as those involved in the conversion of galactose and fructose to glucose[69, 70], and in some oxidative reactions[71]. It may be concluded that, although the sulfonylureas may depress liver glycogenolysis and the effects of glucagon and epinephrine somewhat, this action is not sufficient to explain their blood sugar lowering effect and the liver is probably not a major site of action. This is confirmed also by the fact that, while these drugs lower the blood sugar of hepatectomized dogs[68], they have no effect in severly alloxan diabetic animals and in totally depancreatized animals and men, with intact livers[16, 21, 32, 34, 57, 72-74]. On the other hand hypoglycemia can be obtained in partially alloxanized animals[53] and in animals with as little as one-tenth of their pancreas left[57], suggesting that the action of the drugs depends upon the presence of insulin and may be due to stimulation of insulin secretion, inhibition of insulin destruction or potentiation of insulin action. 3) *Stimulation of insulin secretion.* The injection of IPTD or carbutamide into the arterial supply of the pancreas or into the pancreatic duct results in a fall in peripheral blood glucose, even though the amount injected is insufficient to produce "therapeutic" blood levels of the drug[7, 75]. Similar results were obtained by means of pancreatic-femoral cross-circulation experiment in which it was shown that the blood of the pancreatic, but not of the mesenteric vein of donor dogs treated with carbutamide causes hypoglycemia in recipient animals[76]. These results are consistent with the hypothesis that one of the results of carbutamide injection is the release of insulin into the blood. In most cases the B cells of the treated animals contain a normal amount of granules[52, 53, 76] and of zinc[77] indicating continued function and suggesting that the drug causes insulin secretion rather the release of preformed hormone. This is in agreement with evidence that islet growth may occur as a result of prolonged treatment with IPTD or carbutamide[7, 78]. Increased insulin secretion should result in improved carbohydrate tolerance. Results of these studies are contradictory: some investigators[31, 43, 46, 79-81] reported that treatment with sulfonylurea improves carbohydrate tolerance in normal animals and diabetic patients, other investigators[32, 35, 69, 82, 83] could find no significant differences. 4) *Inhibition of insulin degradation.* Insulin is believed to be de-

stroyed by "insulinase," an enzyme system especially abundant in the liver. The insulinase activity of the liver of animals treated with carbutamide or tolbutamide was found significantly depressed by Mirsky and collaborators[84]. These investigators believe that there are two phases in sulfonylurea hypoglycemia: a first rapid phase due to insulin discharge and a second more prolonged phase due to insulinase inhibition[85]. Other investigators were unable to show a decreased insulinase activity or were able to obtain it only with drug consentrations much greater than those sufficient to lower the blood sugar[86], perhaps because the sulfonylureas are non-competitive inhibitors of insulinase and act as non-specific poisons of the —SH groups necessary for its activity[84, 85]. In addition most[31, 32, 62, 64, 85-88] although not all[33, 89-91] authors believe that the sulfonylureas in therapeutic amounts do not enhance or prolong the effect of single insulin injections, as they should if the distribution of insulin were inhibited. 5) *Insulin-like activity.* Contrary to insulin, tolbutamide does not accelerate the intracellular transfer, the uptake or oxidation of glucose in eviscerated-nephrectomized animals[87, 92, 93]. The effect of carbutamide and tolbutamide on A-V glucose difference is uncertain: while the oral administration does not appear to modify it significantly[61, 82, 94, 95] the intravenous injection causes a marked increase, accompanied by a decrease in serum potassium and inorganic phosphorus. These results are comparable to those produced by the injection of insulin and occur in normal but not in depancreatized subjects[73]. Studies *in vitro* gave contradictory results: according to some investigators[71, 96] the sulfonylureas cause a significant increase in glucose uptake by the isolated rat diaphragm, while other investigators found no significant changes[93] casting considerable doubt on the hypothesis that the sulfonylureas may have a direct insulin-like action on glucose utilization by the peripheral tissues. In depancreatized dogs and diabetic subjects treated with IPTD or tolbutamide the administration of glucose results in an increase of the respiratory quotient, but these experiments lack adequate controls[16, 97]. The concentrations of lactic and pyruvic acids in the blood are not consistently increased by sulfonylurea, as they are by insulin treatment[69, 70, 98, 99]. In addition, while both hypophysectomized and adrenalectomized animals are hypersensitive to insulin, the hypoglycemic effect of sulfonylureas is exaggerated in the adrenalectomized, but not in the hypophysectomized one[21, 34, 55, 100, 101]. It should be pointed out that some of these negative results have been obtained in depancreatized animals, in diabetic patients or in patients receiving intravenous glucose, where stimulation of insulin secretions cannot occur or may already be maximal. In summary it appears that the sulfonylureas may cause insulin secretion, although they do not have all the effects of this hormone. In this re- be compared to that of growth hor- spect the action of these drugs may mone[102, 103]. 6) *Miscellaneous effects.* It has been reported that sulfonylureas traverse the blood-brain barrier very slowly[18], that they cause a decrease in the concentration of blood mucoproteins[81], of total lipids and of cholesterol[104], a decrease, followed by a marked increase in serum sodium and a decrease in potassium, coincident with an increase in liver glycogen[105] and that they reduce the absorption of glucose from the intestine[106]. The administration of sulfonylureas sometimes causes a decrease in circulating eosinophiles, suggesting stimulation of the pituitary-adrenal axis[82]. This may explain the failure of the drug to correct hyperglycemia due to surgical stress[74], the resistance of animals with steroid[57, 107] and metahypophyseal diabetes[100, 108], and the already mentioned hypersensitivity of adrenalectomized animals to the drug[34, 55, 59, 69, 101]. However, the excretion of adrenal cortical hormones does not appear to increase following the administration of the drug[62, 109]. Carbutamide has been used successfully, in conjunction with insulin, for the purpose of inducing therapeutic hypoglycemic shock[110].

IV. Clinical Results

Many thousands of diabetic patients have been treated with sulfonylureas

during the past few years and are being treated now[A, 25, 46, 111-113], for carbutamide and tolbutamide have been approved and are on sale in several European countries. Although many more patients have been treated with carbutamide than with tolbutamide or IPTD, the results appear to be similar[114] and can be summarized as follows: 1) in middle aged, obese diabetics of the lipo-plethoric type of Lawrence a satisfactory degree of control can be achieved in 70-80% of the cases. Usually these patients suffer from mild stable diabetes and have a relatively small insulin requirement. According to some investigators the best results in this group are obtained in patients suffering from diabetes of a short duration[10, 19, 50, 64], while according to others the duration of the disease is not an important factor[28, 115]. 2) Results are less satisfactory in patients below the age of 40 and under the age of 30 results are usually very poor. In children or patients with "juvenile" and "brittle" diabetes with strong tendency to ketosis the results are negative, with rare exceptions[80], and the risk of abandoning insulin is too great to warrant a therapeutic trial[116], unless the patient is under the closest hospital supervision. 3) The drugs are also ineffective, and therefore contraindicated, in depancreatized patients and in patients with ketosis, infections and fever (who frequently also have an increased insulin requirement) and in patient undergoing surgery. 4) The drugs should be considered contraindicated also in hepatic and renal disease, in patients with anemia or leucopenia and in individuals receiving sedatives, transquillizers or under the effect of alcohol[117], at least until their toxicity has been better evaluated. 5) In agreement with the hypothesis that sulfonylureas stimulate insulin secretion, these results seem to indicate that the drugs are most effective in the type of patient who still possesses an appreciable source of endogenous insulin, as indicated by the insulin content of the pancreas[118] or the degree of B cell degranulations[52].

V. Conclusions

1) Sulfonylureas cause marked hypoglycemia when taken orally or parenterally. 2) The most likely explanation for this effect appears to be a stimulation of insulin secretion. (3) If this is correct, chronic stimultion of the B cells by the drugs may lead either to their regeneration or to their exhaustion. These and other possible effects of continued treatment have not been evaluated, as yet. 4) Patients receiving the drug may be only partially controlled and become asymptomatic and the temptation to compromise in order to avoid the use of insulin may be great[27]. This is potentially dangerous since little or nothing is known about the effects of sulfonylureas on diabetic complications. 5) The drugs are most effective in patients who need insulin the least. This makes it very difficult to evaluate their overall effectiveness, since insulin requirements in these patients can be changed markedly by dietary restrictions and weight loss. To quote Best[119], "The only active ingredients of some substitutes for insulin, in certain mild cases of diabetes, have been the general clinical care and the comforting presence of a good doctor." 6) Sulfonylureas are useful investigative tools and, if used under proper supervision, may become very useful drugs for a large number of diabetics.

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THE STATUS OF THE L. E. PHENOMENON

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The discovery of the LE phenomenon in 1948[1, 2] has provided a remarkably specific test for the diagnosis of systemic lupus erythematosus (SLE). The test has been especially useful in the evaluation of vague symptoms and signs such as occult fever, splenomegaly, adenopathy, arthralgias, chest pain, night sweats, weight loss, anemia, leukopenia and thrombopenia. Thus many ill defined disease states have been clarified and therapy more specifically established. It is the purpose of this paper to discuss the characteristics and differentiation of the classical LE cell, and to comment on the mechanism of formation and specificity of the LE phenomenon. Since positive LE tests have been reported in diseases other than SLE, these require special attention. We have had considerable experience with this problem and some of the material will be presented.

The LE Cell

The characteristic LE cell is a mature white cell which contains a large, smoky, homogeneous, purplish staining inclusion body that pushes the nucleus of the white cell to the periphery with a small rim of cytoplasm surrounding the central inclusion mass. (Figure 1.) This phagocytic white cell is usually a neutrophil; however, eosinophils, basophils, monocytes, lymphocytes and even plasma cells may become involved in this phenomenon. The inclusion body is believed to consist of depolymerized desoxyribosenucleic acid, which may be derived from the nuclear material of various cellular elements. This typical cell must be differentiated from cells revealing nucleophagocytosis in which the inclusion mass resembles nuclear material or contains remnants of nuclear material, especially in the periphery (Figure 2). Rosettes consist of a central amorphous mass, surrounded by a cluster of white cells or their nuclei. These rosettes are often found in positive LE preparations together with free clumps of amorphous purplish material. Cells showing late stages of nucleophagocytosis can easily be confused with LE cells, but difficulty can be avoided if the strict criteria of smokiness, homogeneity and purplish staining of the amorphous inclusion body are adhered to before calling the test positive.

There is much speculation as to whether nucleophagocytosis might not be a transition phase in the development of the LE cell. We have found that the finding of far advanced nucleophagocytosis and rosettes makes the preparation very suspicious, and that further search or repeat examination often leads to a positive result.

The LE test can be performed with oxalated or heparinized blood or marrow, but the use of clotted blood[3] has yielded much more sensitivity as well as the finding of more nucleophagocytosis. Although this increased sensitivity is very desirable, it is necessary to exercise caution in order to avoid confusion with nucleophagocytosis.

Mechanism of Formation

The mechanism of the LE phenomenon is still in question. It is believed that a plasma LE factor residing in the gamma globulin fraction of blood proteins is associated with depolymerization of the desoxyribosenucleic acid (DNA) derived from nuclear material, and that the amorphous material so formed is then engulfed by the white cells of the patient or normal individuals. There is also the possibility as postulated by Kurnick[4], that enzyme activity (desoxyribonuclease) may cause depolymerization of DNA because of a lack of an inhibitor substance to this enzyme.

It has long been felt that this phenomenon takes place in vitro. However,

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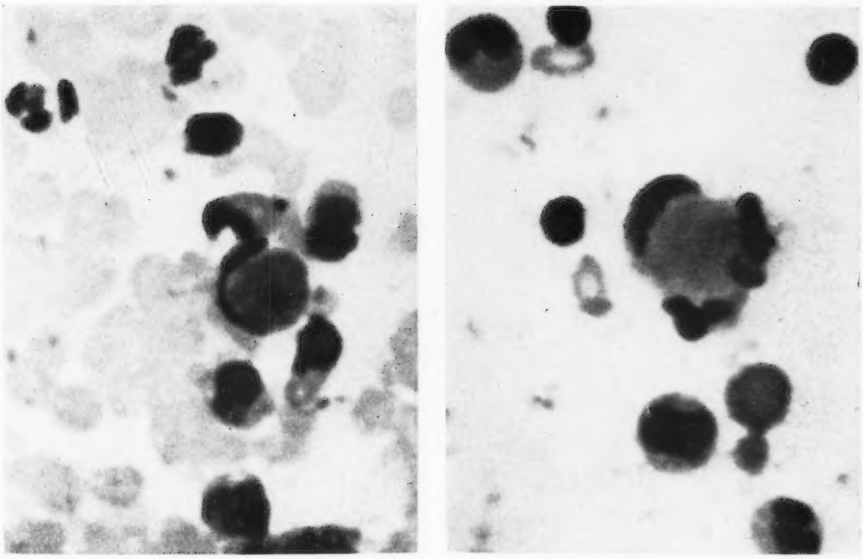

Figure 1. Typical LE cells.

Chomet and associates[5] found the LE cell in the peripheral blood film of a terminal patient with systemic lupus erythematosus (SLE). Inasmuch as hypoxia and stasis were assumed to be present in a terminally ill patient, and since Haserick[6] observed the LE phenomenon in 12-13 minutes of incubation in vitro, our group used this information to demonstrate the LE phenomenon in vivo. This was done by constructing a finger for 20 minutes and studying direct blood films made from the tip of the constricted finger after this period of constriction. (Figure 3.)[7] In this way, both typical LE cells and rosettes were found in the majority of the classical SLE patients studied. It is possible that this method of production of the LE cell in vivo may provide an excellent means of further study of this phenomenon. Some of the factors involved may include white cell injury by hypoxia, prolonged contact with the vascular wall, changes in the blood pH, enzyme activity, and other possible factors. The clotting of blood, the presence of platelets, injury to white cells or the death of these cells may enhance the positivity of the test.

Specificity of the LE Phenomenon

In the earlier years of the development and evaluation of the LE test, most workers were impressed with its specificity for the diagnosis of SLE. Occasional early reports of false positives in such conditions as multiple myeloma,[8] pernicious anemia,[9] leukemia,[10] and dermatitis herpetiformis[9] were difficult to evaluate since the precise characteristics of the phenomenon and the differentiation from nucleophagocytosis were not yet fully understood. Therefore, ingested nuclear material, red cells, and precipitated protein material could have been mistaken for the homogeneous globular mass of the LE cell. However, as refinements of technique were developed, and as the more sensitive clot methods were more widely utilized, unequivocal positive results began appearing in the literature in conditions other than SLE. At first the LE phenomenon was reported in patients with hypersensitivity reactions to penicillin[11] and tetanus antitoxin serum;[13] later other drugs were incriminated. Then positive results began to be reported in conditions related to SLE, such

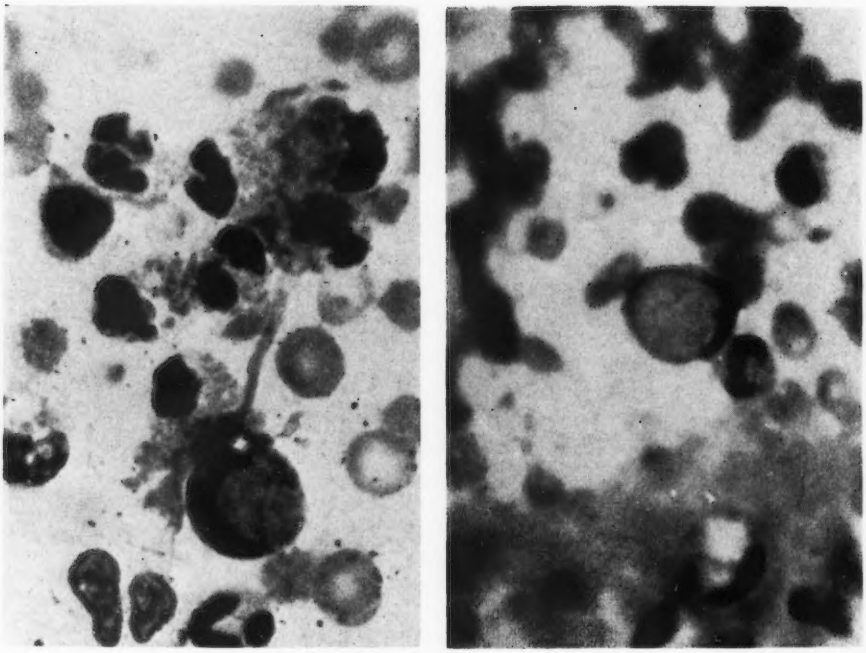

Figure 2. Examples of nucleophagocytosis: (a) Monocyte engolfing nuclear material (Tart Cell). (b) Far advanced nucleophagocytosis with darker outer rim of nuclear material in engulfed material.

as periarteritis nodosa and rheumatoid arthritis. Recently reports have appeared in conditions not closely related to this systemic disease. At first the impression was that these conditions were atypical forms of SLE, especially in the cases of rheumatoid arthritis, but it is becoming apparent that a more realistic approach must be taken in evaluating the instances of positive cases that cannot fit into the natural history and the clinical picture of SLE. It should be stressed, however, that these positive tests are rare in other conditions as is evidenced by the reporting of isolated case reports of such occurrences despite the widespread use of this test. The conditions other than SLE acceptable to us as being occasionally associated with a positive LE test include:

1. Penicillin[11, 12] and tetanus antitoxin serum sensitivity.[13]
2. Hydralazine administration with "SLE-like syndrome."[14, 15, 16]
3. Phenylbutazone sensitivity.[17]
4. Periarteritis nodosa.[18]
5. Thrombohemolytis thrombocytopenic purpura.[19]
6. Rheumatoid arthritis.[20]
7. Post-necrotic cirrhosis.[21, 22]
8. Tuberculosis*[23, 24]

In reviewing these results, one is impressed with the fact that almost all the examples of positive LE tests are in the "hypersensitivity" group of diseases, including drug reactions, collagen diseases, and hyper-globulinemic states. We have found positive results in our laboratory in rheumatoid arthritis, thrombohemolytic thrombocytopenic purpora and questionable cases of tuberculosis.

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* There is still a question in our minds as to whether these patients have SLE with complicating tuberculosis in spite of the fact that pathologic findings for SLE were absent.

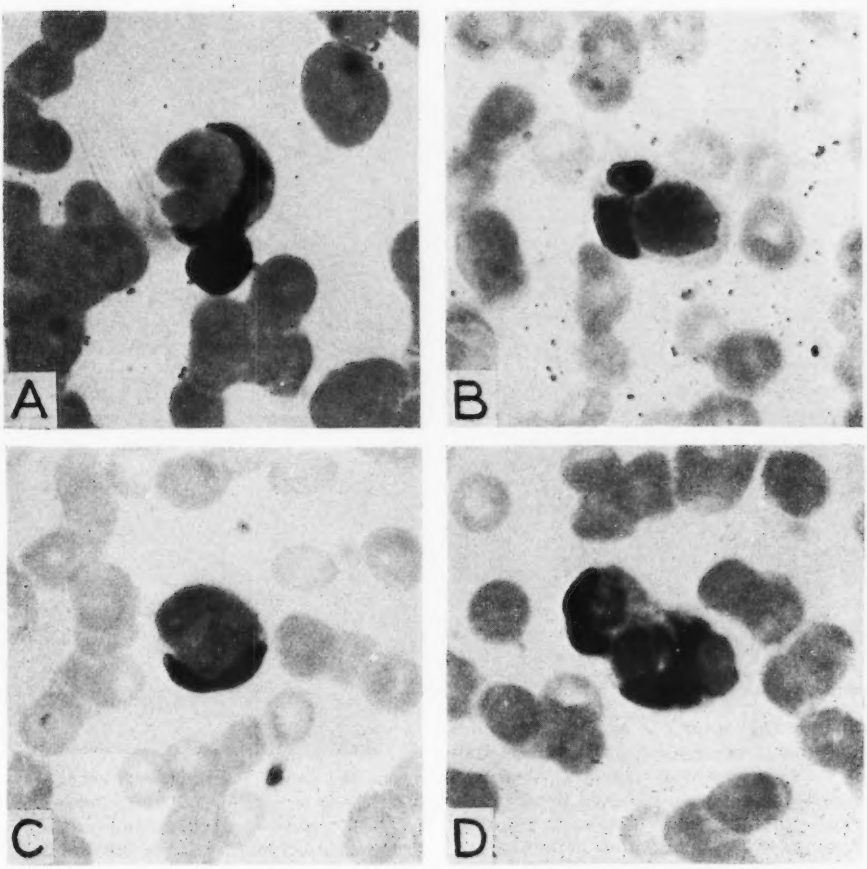

Figure 3. LE cells found in vivo with finger constriction technique (reproduced through courtesy of Journal of Laboratory and Clinical Medicine from "Time Factor in Production of the LE Phenomenon," Sickley, J. F., Friedman, I. A., and Feldhake, C., 47:306, 1956).

Rheumatoid Arthritis[20]

Ninety-one cases of typical chronic rheumatoid arthritis (Fig. 4) were studied of which 25 patients were found to have positive LE tests (Fig. 5). These patients were studied extensively by clinical and laboratory means including electrophoretic studies of the serum, sheep cell agglutination tests and histologic examination of lymph nodes, spleens, and subcutaneous nodules. The results of these determinations were compared with those in a group of rheumatoid patients with negative LE tests. There was no clear-cut differentiation clinically or by laboratory means between the positive and negative groups. However, the positive patients revealed a higher incidence of rheumatoid nodules, Felty's syndrome, and elevated gamma globulin as determined by serum electrophoresis. None of the positive patients presented the picture of a pure rheumatoid spondylitis but consisted primarily of peripheral rheumatoid arthritis or combined arthritis. Therapy with steroids did not influence the incidence of positive preparations in this study. The positive patients had their disease for many years and showed none of the stigmata of SLE at any time

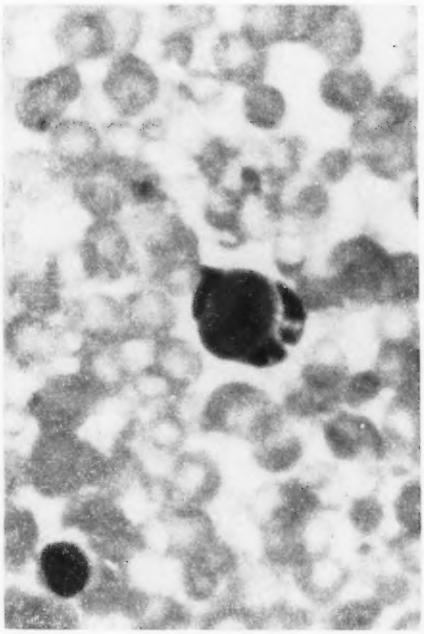

Figure 4. Typical LE cell found in a patient with classical chronic rheumatoid arthritis.

during the study. It is felt, therefore, that classical rheumatoid arthritis may have a positive LE test and, if this is found, these patients should be given the same therapy and prognosis as other patients with rheumatoid arthritis.

Thrombohemolytic Thrombocytopenic Purpura[19]

A patient with thrombohemolytic thrombocytopenic purpura with typical neurologic findings, hemolytic anemia, and thrombocytopenic purpura was studied. This patient has been in remission for almost two years since the spleen was removed and histologic examination revealed the classical lesions of this disease (Figure 6). A positive LE test was found eight months after splenectomy. However, the patient has not manifested any of the classical clinical or laboratory features of SLE, nor did histological review of the spleen reveal any suggestive findings.

Tuberculosis

Two patients from the chest hospital

Figure 5a. Photograph of severe rheumatoid arthritis of hands with subcutaneous rheumatoid nodules on forearm and in olecranon bursae.

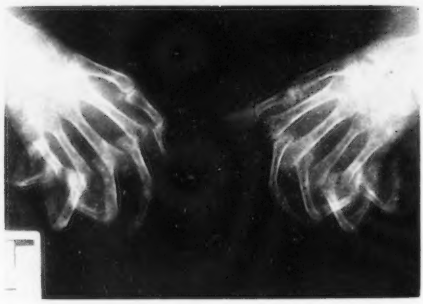

Figure 5b. X-rays of same patient's hands showing changes of rheumatoid arthritis.

have been found to have positive LE tests without any stigmata of SLE. However, there is much question in our minds as to the significance of these findings, since these patients may eventually develop manifestations of SLE with complicating tuberculosis.

Discussion

Many workers have stressed the specificity of the LE phenomenon. Indeed, despite the exceptions noted above, this is a remarkably consistent and reliable test for SLE when the clinical picture coincides. However, it is dangerous to conceive of any test being specific since our clinical thinking would be narrowed, and we would tend to find the diagnosis to a single laboratory procedure. If the test were considered infallible, such diseases as rheumatoid arthritis patients

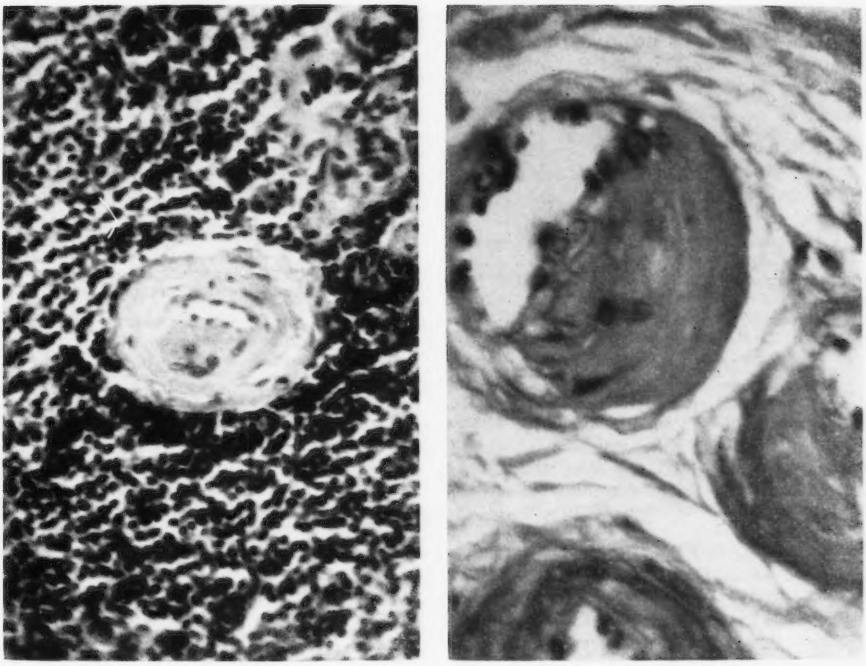

Figure 6. Classical vascular lesions of thrombohemolytic thrombocytopenic purpura. Spleen: a. Low power, b. High dry.

would immediately be considered cases of SLE when a positive LE test is found. This would be especially true if these patients demonstrated fever, loss of weight, or any pleural and renal findings. It is known that these abnormal findings may occur in long-standing rheumatoid arthritis during the course of the disease and do not necessarily indicate SLE. It would be more reasonable to take the attitude that this is an accurate test when it fits with the clinical picture and to continue approaching the patient's diagnosis and therapy on the basis of past experience and the natural course of the disease.

On a theoretical basis, it is intriguing to consider all these conditions as those of hypersensitivity having a common etiologic background with a spectrum of activity, chronicity and response of the target organs. This can explain easily overlapping of findings as is frequently seen especially in regard to SLE and rheumatoid arthritis. Specific proof of this inter-relationship is one of the most fascinating problems of present-day basic research.

Summary and Conclusions

1. The study of the status of the LE phenomenon has been discussed in regard to characteristics of the phenomenon, present ideas of the mechanism of formation, and specificity. Also, the significance and interpretation of positive tests in diseases other than SLE was reviewed.

2. This laboratory has found positive results in conditions other than SLE which include rheumatoid arthritis, thrombohemolytic thrombocytopenic purpura and questionable cases of tuberculosis.

3. It is felt that, despite positive findings in other disease processes, the LE test is a remarkably consistent and useful tool in the diagnosis of systemic lupus

erythematosus. However, it is stressed that the finding of positive LE tests in conditions other than SLE should not lead the clinician to consider these patients all as having one disease because of a single laboratory finding.

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DIFFERENTIAL DIAGNOSIS OF DISEASES OF THE MOUTH

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Although the study of diseases of the mouth is within the scope of stomatology, changes of the oral cavity, when properly interpreted, may offer valuable clues for differential diagnosis of many conditions.

Inflammation of the mucous membranes of the oral cavity, stomatitis, glossitis and gingivitis may be due to mechanical factors (ill fitting dentures, carious, broken teeth, etc.) to thermal or chemical irritation or poor oral hygiene. More commonly these changes are among signs and symptoms produced by 1) nutritional, 2) infections, 3) endocrine, 4) hematopoetic, 5) allergic and 6) systemic disorders. Nutritional disorders due to either insufficient caloric intake or to lack of some specific factors in a caloric adequate diet, are known as primary nutritional deficiencies. Secondary or conditioned deficiencies are produced by diseases interfering with proper breakdown, absorption or utilization of essential food elements.

At times changes of the oral mucosa, tongue and gums are characteristic enough to reveal a particular deficiency. However, it is known today that single deficiencies are rare or not existing and that practically in every nutritional disorder, in spite of the fact that signs or symptoms point only to one, multiple deficiencies exist.

Malnutrition of short duration may produce atrophy and disappearance of the papillae and occasionally ulcerations of the tongue and lips. In chronic nutritional depletions a magenta discoloration of the mucous membranes indicates deficiency of riboflavin and possibly of pyridoxine. Cheilosis or perleche, a superficial maceration and fissuring of the angles of the mouth, believed to be characteristic of riboflavin lack is also present in other deficiencies and is seen most frequently in hypochromic anemias.

In pellegra and sprue (tropical or nontropical) the tongue and buccal mucosa around the Stenson duct are scarlet red and an extreme soreness of the mouth is associated with increased salivation. In severe cases, ulcerations covered by a grayish slough and due to secondary infection with Vincents organism are also found. Lack of essential amino acids and nicotinic acid is supposed to be responsible for these changes.

The oral manifestations of ascorbic acid deficiency are well known and are characterised by spongy, hyperemic, ulcerated, bleeding gums and loosened teeth; eating and chewing is difficult and extremely painful.

Infections may produce a variety of manifestations in the mouth, some of which are easily recognized and well known (strawberry tongue of scarlet fever, the Koplik's spots in measles, etc.) The fact that petechvial hemorrhages of subacute bacterial endocarditis can be spotted on the hard palate and that a reddish vesicular eruption of the oral mucosa is an early sign of infectious mononucleosis is not commonly appreciated.

The primary lesion of syphilis may present itself as a painless indurated papule or ulcer of the lips, tongue or angles of the mouth. Identification of the spirochete by darkfield examination differentiates the lesion from a carcinoma; the Wasserman test at this stage is negative and of no help. The secondary lesions of lues are scattered, painless papules which ulcerate eventually and are covered by a grayish membrane; they are often mistaken for a Vincent's infection. The tertiary lesion, the gumma is most frequently seen on the hard palate and on the tongue and may mimic carcinoma. It can be differentiated from the latter only by biopsy, a positive serology alone is not sufficient for diagnosis.

A late syphilitic lesion of the tongue and buccal mucosa is leucoplakia. It is

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a whitish, irregular and indurated patch at times fissured or ulcerated. Most leucoplakias are not syphilitic and although considered precancerous lesions they rarely become malignant.

Tuberculous ulcers of the mouth are not frequent and occur mostly on the dorsum of the tongue. They are painful lesions of irregular shape with soft, not indurated edges seen in far advanced pulmonary or pharyngeal tuberculosis and produced by implantation of the bacillus in a traumatized tongue. X-ray of the chest, sputum and smear examinations help verifying the diagnosis.

A relatively common infection of the oral cavity is known as trench mouth, ulcero-membranous stomatites or Plaut-Vincent's angina. It is produced by normal soprophytes of the mouth, the fusospirochetal symbionts which may act as secondary invaders when the mucous membranes are affected by local or systemic disturbances (poor oral hygiene, vitamin deficiencies, heavy metal poisonings, etc.) The infection is characterized by patches of greyish necrotic membranes, which removed by force, leave a bleeding surface; the regional glands are enlarged and tender and in severe cases fever and constitutional symptoms are present. Smears identify easily the organisms.

Moniliasis develops in debilitated patients with poor oral hygiene and in malnourished infants. The lesions produced by this infection are painless, elevated white areas, often mistaken for milk curds; budding spores of a yeast-like organism (candida albicans) are readily recognized in smears and cultures. Candida albicans, the fusospirochetal symbionts and a great variety of other organisms are present in the normal oral cavity, but because of a symbotic and antibiotic relationship none of them become predominant. However, and disturbance in this cooperative existence which may be caused by local, excretary, systemis factors or prolonged use of antibiotics, can upset the balance and tip the scale in favor of one group of organisms which grow then luxuriosly and becomes pathogenic.

The hairy black tongue seen after prolonged use of penicilin, the severe diarrhea with ano-rectal symptom after the administration of wide spectra antibiotics (antibiotic colitis) are believed to be largely due to an overgrowth of candida albican in the G.I. tract. Severe infection with pseudomonas produced under similar conditions is another example of the ever increasing incidence of iatrogenic diseases.

A grave streptococcic infection of the floor of the mouth and root of the tongue associated with a hard wooden infiltration of the submaxillary region is known as Ludwig's angina. Early recognition and treatment of this most serious disease which may threaten the life by glottis edema, is of paramount importance.

Disorders of the hematopoetic system and blood dyscrasias manifest themselves occasionally by lesions of the oral cavity. Best known are the smooth atrophic and sore tongue of pernicious anemia and the fissures at the corner of the mouth found in the hypochromic anemias. The maroon colored lips, tongue and mucous membranes of the mouth of polycythemias are often mistaken as being due to cyanosis. Deep ulcerations with constitutional symptoms may be produced by a granulocytosis of different origin or by acute leukemias with a decreased number of normal functioning white cells. Infiltration of the gums and tonsils due to excessive accumulation of immature white cells in the tissue are encountered in acute and chronic leukemias. Severe oral bleeding with formation of hemorrhagic blebs is characteristic of thrombocytopenias and may at times also occur in leukemias. Hemorrhages due to hemophilia or Vitamin K deficiencies are rarely seen in non-traumatized oral cavities. Multiple dilatations of capillaries and venules of the mouth are occasionally the only evidence of the hereditary, hemorrhagic telengeiectasia (Osler-Weber-Randu disease).

Glossitis, atrophy and soreness of the tongue with pallor of the mucous membranes have been described as Plummer-Vinson syndrome or sideropenic dys-

phagia. It is a type of non-deficiency anemia in which dysphagia is attributed to achalasia or to a peculiar web formation in the upper part of the oesophagus. A higher incidence of cancer of the pharynx or oesophagus is reported to be another feature of this condition.

Careful inspection of the mouth may at times offer differential diagnostic clues in endocrine, metabolic and systemic disturbances.

Prolonged administration of estrogen and progesterone produces occasionally a peculiar hyperplasia of gingival tissue or scattered ulceration of the oral cavity.

Pigmentation of the oral mucosa or small pigment dots present on the lips and periorally may alert us to look for Addison's disease or congenital familiar polyposis of the G.I. tract; a yellow discoloration of the hard palate is an early sign of a subclinical jaundice.

Macroglossica, a flabby, large tongue may be due to hypothyroidism, acromegaly or primary amyloidosis.

Stevens-Johnson's and Behcet's syndrome two mucocutaneous systemic diseases of unknown origin, produce among other manifestations (erythema nodosum multiforme with respiratory involvement, conjunctivitis, iritis, balanitis, etc.) severe recurrent stomatitis with ulceration of the lips and tongue.

Lesions of pemphigus and lichen ruber planus may occasionally be seen in the oral cavity before other areas are involved. Hypertrophied sebaceous glands in form of pale or whitish spots of the lips and buccal mucosa are known as Fordyce disease (harmless condition).

Stomatitis, gingivitis, saliorrhea with secondary infections may occur in conditions in which the oral mucosa attempts vicarious excretion of noxious substances of exogenous or endogenous origin. The most common exogenous substances are lead, bismuth, arsenic, silver, iron, dilantin, etc., irrespectively whether introduced orally or parenterally. Some of these substances produce characteristic lines on the margin of the gums (lead and bismuth lines) others cause pigmentation (argyria) or inflammation of the mucosa. From the endogenous substances eliminated by the oral mucosa urea is responsible for urenic stomatitis and certain amines are possibly the cause of fetor hepaticus.

Allergy of the mouth manifests itself most commonly by angioneurotic edema or aphthous stomatitis (cancer sores). These lesions may be produced either by direct contact, or as reaction to an ingested allergen; eggs, cheese, chocolate, nuts, shellfish and barries are the most common offenders. The lesions have a tendency to recur, are painful and difficult to treat; it is doubtful whether allergy alone is the responsible factor.

The neoplasms of the oral cavity are benign or malignant and some of the latter may develop from the so-called precancerous lesions.

The benign tumors are of the same variety as found elsewhere in the G.I. tract and the more common ones are papillomas, lymphangiomas, neurofibromas and lipomas. They may become of clinical importance when by increase in size or chronic irritation, they interfere with the normal function of the mouth.

Every tumor or ulcer of the oral cavity or tongue should be considered malignant until proven otherwise by careful histologic examination.

The squamous cell carcinoma of the tongue and lips is the most frequent malignant lesion although sarcomas of the tongue or gums (epulis) may occasionally occur. The carcinoma of the oral cavity may present itself in the early stage as an innocent looking induration or nodle which changes later to a chronic non-healing ulceration accompanied by swelling of the regional glands. No definite characteristics help differentiate the malignant from the benign lesions (traumatic ulcers, ulcer-membranous stomatitis, syphilis, tuberculosis, etc.) and therefore only biopsy and histologic examination should be relied upon in establishing the diagnosis.

Leucoplakia, syphilis, papilloma and chronic ulcers due to trauma or irritation

are considered precancerous lesions; although some of them may become malignant, it is impossible to predict which and when they will do so. Only careful observation and repeated histologic studies can determine the appropriate and necessary therapeutic procedures. Papillomas of the tongue should always be removed.

The coated tongue, considered of great diagnostic importance by past medical generations, is a nonspecific condition not characteristic of any particular disease. The shedding of the surface epithelium is a continuous self-cleansing process maintained by the movement of the tongue and by the friction of the organ with other structures of the mouth. This mechanism is normally interrupted by sleep (the coated tongue in the morning) but may be interfered with during waking hours by a great variety of local and systemic disturbances and result in a coating consisting of desquamated epithelium, particles of food, bacteria and fungi.

Xerostomia (dry mouth), glossodynia (sore tongue) and bitter taste in the mouth are nonspecific sensations complained of by diabetics, by patients with anemias, vitamin deficiencies, arteriosclerosis, nephritis, by women in menopause and by neurotics.

These sensations are occasionally due to mechanical irritations (ill fitting dentures, broken teeth, etc.) or to galvanic currents from different metallic fillings; in a majority of cases no changes are found in the oral cavity responsible for their presence.

PSYCHOPHYSIOLOGICAL MEDICINE:

A Practical Approach to Functional Diagnosis In General Practice

ROBERT JEANS, M.D.†

Sir William Osler wrote, "In the physician and surgeon no quality takes rank with imperturbability . . . " (*Aequanimites,* Blakiston, 1947). If the factors which disturb this essential quality were to be listed, for most physicians in general practice the problem of functional diagnosis would certainly head the list. This is especially unfortunate in view of the fact that a large proportion of general practice consists of psychogenic disorders, and most of it involves some functional component, whether primary, secondary or in combination. This article is an attempt to show that physicians can maintain an unruffled calm in the face of non-organic illness with tools already in their hands, or at least, readily accessible.

The brain reacts to stress* in a characteristic way, depending on the severity of the stressful stimulus. The processes evoked by stressing the brain may be as varied as the stresses themselves. Basically, they serve to regulate the brain's functions within a range compatible with life. If this basic condition is satisfied, the brain further attempts to regulate itself within a range compatible with conscious functioning. Safe in this regard, the brain has more subtle homeostatic mechanisms which act to protect the person's conscious waking state and keep it within the range of what is felt to be socially acceptable. If all these mechanisms are operating effectively, the brain can react to a stress by meeting it realistically and resolving the problem with only a minimum of anxiety. But pathologically they may operate excessively to maintain too great a constancy despite a changing environment, giving rise to psychotic states, or may overregulate with regard to internal standards of social acceptability, giving rise to neurotic trends. Psychophysiological reactions tc stress are most marked within the neurotic group—i.e., those with whom the general practitioner is most likely to deal.

Stresses may be actual or symbolic, but if one listens long enough the patient will tell you (even though he does not see it himself) what he is reacting to, how he became conditioned to react in this way, and what the earlier predisposing factors were. The physician's own feelings are the most sensitive instrument for detecting those of the paient; but the instrument requires sharpening, and impatience or a routine approach dulls it. One way of eliciting the stress history along with the medical is to use the technique of *associative anamnesis.* Essentially, this consists of the following:

1. Let the patient tell his story in his own way. He will tell you what his consciousness permits him to consider the chief complaint. This, however, is only the *explicit chief complaint;* more imporant and more difficult to arrive at, the *implicit chief complaint* must be arrived at by the physician by listening and noting his feelings and reactions to what the patient tells him.

2. Note particularly any discrepancies in what the patient has related, or between what he has related and what the physician sees, feels or thinks is so. These may be extremely valuable clues, because they tell the interviewer that the patient, in order to avoid anxiety, is distorting or avoiding something which nevertheless is acting as a stress.

3. Questions should be directed at the discrepancies which have been noted, or at any points of unclarity or gaps which the patient has left in his story.

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* "Stress" can be considered (as it is generally in medicine) to be any influence which disturbs the stability of the internal environment and therefore evokes the activity of homeostatic devices of the organism to restore the equilibrium.

The physical examination provides further opportunity for understanding the patient as a complex, socially conditioned person with a certain personality and sets of attitudes or reactions which he may not be ready to verbalize. Some noteworthy clues in this regard are: excessive prudishness, or exhibitionism, denial of illness, obesity, pupil size, sweaty palms, sphincter tonus, and—most important—facial expression.

A large proportion of the information upon which diagnoses and treatment are based will most often be in the history elicited from the patient. It is essential to know whether the history is reliable by some method better than guesswork. It is quite valuable to cultivate the habit of estimating the *mental status* of the patient during the course of history taking. To do this well requires practice, but the reward is that it spells the difference between the wise physician and the proficient technician. Here is one capsule summary of categories of observations which should be considered in estimating mental status:

1. General Behavior: apearance, mannerisms, neatness
2. Intellectual level: logic, information and ability to express himself
3. Sensorium: time, space and self-orientation; memory and ability to use what is recollected
4. Emotional state: the main parameters are depression-elation, dissociation and anxiety. Note any flatness or inappropriateness of emotional reaction. Be alert for more or less hidden signs of depression, such as anorexia, constipation and matutinal (early morning) insomnia—the so-called "depressive triad."
5. Note any special symptoms such as hypochondriacal preoccupation, phobias.
6. Insight: what does the patient think of his illness, his prognosis, and what are his attitudes toward the examiner.

There are certain alterations in mental status to be observed in anyone who is ill, since illness of whatever etiology is a stress, a threat to the functional integrity of the patient. Some degree of anxiety and regression occurs in any illness and so is present in any patient. It is important to estimate what degree and how appropriate the degree of reaction to the stress of illness is, and then to account for any functional abnormalities in positive and precise terms. The "functional overlay" label too often overlays a general avoidance of a systematic approach to functional illness, despite the fact that it makes up a large proportion—many say the bulk—of a general practice.

Actually, the medical frame of reference applies to functional disorders as well, and, as I will attempt to show, one needs only a fairly intact set of human feelings and the basic scientific information generally known and accepted in medicine today to be able to deal with those non-psychotic functional disorders making up so much of the patient population. If one takes the trouble and initiative involved in making a positive diagnosis, the apparently difficult (and therefore commonly oversimplified) problem of when to refer to a psychiatrist will not seem so imposing. Psychodynamics and diagnosis cannot be counterposed (except by those who know the significance of the current diagnostic labels so well that they are working to change some of them). Diagnosis may rest on extensive psychodynamic formulation or on a brief history and physical. The point of emphasis here is the latter, since this approach is accessible to the general practitioner in a short time by dint of his own efforts.

In general, the psychotic patient offers no great diagnostic problem for the general practitioner, and once the diagnosis is made referral for psychiatric care is indicated. Much more variegated and complex are the problems of neuroses, personality disorders, psychophysiological autonomic and visceral disorders pathoneuroses and transient stress reactions. I will not try to deal comprehensively with each entity or list the

entities in any detail. Standard references include this information. What I will try to do is provide some points of differential diagnosis and interrelationships between the standard entities which may make the brief diagnostic work-up more of a possibility for the general practitioner by bringing it on to ground which he can properly claim is his own.

Anxiety reaction 000-x01*

Anxiety, the simplest functional disorder, is also the normal reaction of the central nervous system to stress. Thus it is a "symptom" which everone has experienced to one degree or another. Rollo May defines it is "the apprehension cued off by a threat to some value which the individual holds essential to his existence as a personality." It is characterized by a subjective feeling of dread and peripheral discharge phenomena, predominantly sympathetic but also parasympathetic. Because anxiety is characterized by dilation of the pupils, sweating of the palms, tension, restlessness and resistance to sedation, it has been assumed that central physiological change would be found to be an increased excitability of the brain. In actuality, the opposite is true. (See Jeans and Toman, Arch. Neurol. Psychiat. 75:534-547, May, 1956.) Anxiety decreases the excitability of the cerebral cortex. Studies on stressed mice confirm this fact.

The fact that stress gives rise to inhibition of cerebral cortex implies a negative feed-back circuit which functions as a kind of reflex gyroscope for the conscious brain, stabilizing it against a change in the direction of sleep or seizures. Evidence points to the corticofugal activation of the diffuse projection fibers of the thalamus as the tracts involved. At lower levels, anxiety enhances conscious activity to a certain degree, alerting, sharpening perception, memory and the use of learned material. The pulse quickens, blood is diverted from GI tract to voluntary muscle, clotting time shortens, the liver liberates glucose, the organism is made ready for flight or fight —against something specifically conditioned for the individual and thus to another person it seems that there is nothing to fear. This illustrates the fact that a symbolic threat can have as powerful a physiological effect as a realistic threat.

Above a certain intensity the activity of the anxiety, gyroscope ceases to be of any advantage to the conscious purpose of the patient. It transcends the range of "signal anxiety" or conditioned inhibition required for effective learning, and the inhibitory effect furthermore disperses and desynchronizes the electrical activity of brain, and also *dissociates* the functional activity of different cortical areas. This *dissociated reaction* (100-x02) may result in aimless running, "freezing," stupor, fugue, amnesia, dream state, somnambulism, etc. *Gross stress reaction* (000-x81) quite likely is on the same basis, as well as depersonalization, derealization and stunned reactions.

One step further on the increased activity of the anxiety mechanism no longer functions on the level of protecting consciousness but life itself, and the individual faints. That this is not stretching the theory of the inhibitory effect of anxiety is attested to by Cannon and others who have described death as a result of cardiovascular collapse, central neurogenic shock. Cannon points out that even this extreme degree of anxiety which is fatal fits the definition of anxiety as a reaction to a symbolic threat (See W. B. Cannon, *Bodily Changes in Pain, Fear, Hunger and Rage,* 2d Ed., New York, 1927): "Voodoo death," as practiced in Haiti at one time; the witch doctor pointed a stick at the condemned man, whom the gods are supposed to strike dead. And, from maximal anxiety, the man promptly died.

Persistent, and therefore relatively mild levels of "signal" anxiety are accompanied by a number of physiological changes as well. Psycho-physiological reactions characteristic of prolonged anxiety are a readiness to respond to consciously or unconsciously perceived

* Code numbers correspond to 1955 A.P.A. suggested revision of the official nomenclature of diseases of the A.M.A.

stress with tachypnea (anxiety alone may be an adequate cause for hyperventilation syndrome), tachycardia, palpitation, temporary arrhythmias, even ECG alterations of relative myocardial insufficiency; (these changes, or phobias of efforts or situations provoking them, may be at the basis of the entity known as "neurocirculatory asthenia," which should be designated "psychophysiologic cardiovascular reaction" instead); polyuria, diarrhea, increased BMR, increased conjugation of sodium benzoate into hippuric acid by the liver (indicating that liver function is altered by anxiety), Thorn test indicates increased pituitary-adrenal axis activity, hyperinsulinism (which may assume the degree found in clinical cases of "spontaneous," or psychogenic hypoglycemia). No doubt this list is incomplete.

If the simplest CNS reaction to stress can be associated with psychophysiological alterations in such varied and significant areas as those listed above, it is not surprising that the psychosomatic approach has gained ground in recent years. By including the CNS in the physiological approach of general medicine to a greater degree, it is quite possible to avoid the extremes which have made many physicians fail to use their own certain knowledge regarding psychophysiological interrelationships.

W. Horsley Gantt of Johns Hopkins has described the phenomenon of *schizokinesis* on the basis of extensive experimental and clinical data. By this term he designates the autonomic portion of a conditioned reflex remaining in full effect, or even becoming enhanced after the conditional reflex itself has ceased to have any observable motor component. Inhibition may remove the motor or conscious portion of the reflex in humans, but the autonomic portion continues to operate for prolonged periods, even indefinitely. Thus, he concludes, people show not only psychophysiological reflexes as a result of some emotion they are experiencing at present, but in addition they are museums of previously adaptive psychophysiological reactions which are not necessarily geared to present needs. Thus, anxiety of the signal (conditional) type may have such an effect long after the person has lost any conscious component of an anxiety reaction, and work-up may consist of eliciting the history of an anxiety attack a year ago without recurrence, and then identifying the current psychophysiological relics of it, since they too may be extinguished if they are not reinforced and are prevented pharmacologically from reinforcing themselves.

Conversion reaction (000-x03) so efficiently excludes anxiety from conscious perception that it is said that hysterical patients have "la belle indifference," while the conflicting motivational patterns of the cortex compromise on a kind of "truce line," which should be traceable on the surface of the hemisphere to those areas which would produce the characteristic symptoms of paralysis, anesthesia or dyskinesis. Rather than fearing a symbolic threat from outside, the hysteric reflexly—and thus, unconsciously—inflicts a symbolic lesion on himself which at the same time symbolizes the wish which had to be inhibited. Some psychophysiological skin reactions are associated with hysterical disturbances. Atopic dermatitis tends to be more severe and prolonged in hysterical patients. This is one *apparent* exception to the rule that links the severity of psychophysiological reactions to the severity of the neurosis.

Phobic reaction (000xx04) is characterized by the displacement and encapsulation of anxiety in some sort of conditional symbol formation, so that the patient has an irrational fear of venereal disease, dirt, closed spaces, height, people in crowds, etc. Children often choose animals, which are recognizably like a parent in some respect. Every irrational fear is, in some way, as Freud wrote, a repressed or inhibited wish. By the process of taking precautions to avoid the feared things or situations, phobic patients may develop more and more phobias (the phobic reflex becomes generalized) and the avoidance and preoccupation may become more firmly conditioned until obsessions and compulsions

develop. This progression from labile to fixed symptomatology is frequently seen clinically.

Obsessive-compulsive reaction (000-x05) is characterized by the fixity of the subjective symptoms, on the one hand, and by the lability of the disinhibited autonomic reflexes on the other. Anxiety, as we have seen, is objectively inhibitory in its effect on cortex; but there are different kinds of inhibition at different levels. The morbid preoccupation and rumination of obsessive neurotic patients deals with ideas regarded as least desirable consciously—"the farthest thing from my mind, Doc"—(and therefore most inhibited); the compulsions are exaggerated and fixed forms of the learned avoidance reactions which phobic patients develop to the symbolic cues of anxiety. In the obsessive-compulsive reaction, anxiety is great enough to bring about the dissociative reaction sometimes seen in acute anxiety attacks. But conditioning and learning serve, as always, to reduce the tension; the patient learns to regard both dissociated patterns as "threats from outside" and the limitation of his conscious control serves to relieve him of the responsibility for deciding how the conflict should be resolved. It is noteworthy that compulsive personalities and obsessive-compulsive neurotics show the most severe psychophysiological disturbances, i.e. that the neurotic disturbance with the greatest degree of persistent and extensive inhibition of the cerebral cortex shows the greatest degree of disinhibition of subcortical centers. The most typical autonomic dysfunctions seen in this group are cardiovascular: tachycardia, transient elevations of blood pressure; skin; dermatographia (more marked than with hysterical patients); some milder forms of atopic dermatitis; migraine, constipation, and various spasmodic disorders of viscera.

Gantt's concept of schizokinesis was derived from laboratory experimental work with dogs, but it is interesting that the empirical facts in regard to obsessive-compulsive reactions and their associated psychophysiological disorders largely confirm his idea. Psychosomatic theory in regard to the problem of hypertension has stressed the role of repressed hostility in the etiological chain of events, but clinicians often reject this as lacking in practical value (if it is really repressed — unconscious — they will not have the time or presumably the tools to find it). However, as we can now see, any anger in the presence of the kind of cortical dynamics seen in the obsessive-compulsive reaction would be blocked by the limitation in conscious control of motor functions, whether it is conscious or unconscious, and the result would be that cortical inhibition of the anger reflex would disinhibit the autonomic reactions associated with anger and produce an exaggerated and prolonged transient elevation of blood pressure. Ordinary anger may produce a transient elevation, but there is no apparent tendency for this to become sustained per se. While this psychophysiological concept is certainly not the established etiological mechanism in essential hypertension, it does have the advantage of allowing the physician to study and evaluate the problem for himself in ways with which he feels—or should feel—familiar.

Depressive reaction (000-x06) is characterized by a reaction of the patient to stress in which the symbolic threat is felt to be within the individual himself, although the anxiety is "bought off" by a spurious kind of exchange: retrograde self-condemnation permits present violations without anxiety. This kind of depression is always associated with some precipitating event to which the patient overreacts because of ambivalent feelings in regard to the loss he has experienced. The threshold to pain is lowered. Gastro-intestinal motility is decreased. The BMR is lowered, and the patient is less inclined to be with people or to engage in any activity. There are frequently many small bodily complaints, but if the depression is really of neurotic degree there should be no delusion either of guilt or bodily degeneration. Some have considered depression to be simply the reflex activation of homeostatic processes designed to protect the organism from an anticipated situation of deprivation, al-

though the deprivation (unlike the fairly uniform basis for hibernation in certain animals) which is expected by the guilt-ridden human being is of an inconsistent and individually conditioned kind which he experienced from a parent or parent substitute early in his life. Since self-esteem depends on willed action according to a plan which accords with the conscious and unconscious dictates of a patient's conscience, the tendency to inaction is not favorable to rapid recovery. But neither is the avoidance hyperactivity of the hypomanic.

Depression is a passive way of coping with a stress, and includes inevitably some sort of inhibition against putting a plan of action into effect which would satisfy the demands for realistic solutions compatible with the person's super-ego (consisting of various patterns of conditioned inhibition, to some degree excessive). Thus, often in a depressed person or one with a tendency to depression, what one may find in the way of psychophysiological disturbances are those involved in basic dependency needs and the way in which they were satisfied or frustrated at the anxiety-provoking crisis in the development of the individual early in life. The specificity of such conditioning, as well as the mixture of feelings, the periodicity of cyclic functions, etc., may account for the fact that bulimia and anorexia are both considered symptoms of depression. Obviously bulimia has more active and aggressive implications.

Fenichel's chapter on "The Nature of the So-Called Psychosomatic Phenomena" in his book, *The Psychoanalytic Theory of the Neurosis* (New York, Norton, 1945), contains one of the clearest discussions of the clinical distinction to be made between conversion reactions and psychophysiological reactions of a non-symbolic kind. His concept of "affect equivalent" is roughly the same as Gantt's "schizokinesis": the autonomic and peripheral consequences of a feeling which no longer resides in the conscious and uninhibited group of cortical conditioned reflexes. In peptic ulcer, for instance, the clinically recognizable disease is not the pre-ulcer state of reaction to stress in which the psychic secretion of gastric juice and gastrointestinal motility is increased in anticipation of the symbolic feeling—gratification of dependent feelings linked with being fed and feeling reassured—which the patient has been seeking in vain. It is a diagnosis which depends on the finding of the organic consequence of something producing these pre-conditions. If the pre-ulcer overactivity is allowed to persist for very long, it becomes the individual's characteristic reaction to stress and makes treatment a difficult and prolonged process.

The greater inhibition of cortex by stress, the greater the peripheral "release" phenomena. Conversion reactions are focal inhibitory states of motor or sensory cortex serving a symbolic purpose. Symbolic processes are confined to the cerebral cortex, and the hysterical limitation of function is relatively free of anxiety because it inhibits just that motor or sensory function which might otherwise cause anxiety. Some psychophysiological reactions may occur in conversion hysteria, but obsessive-compulsive and depressed neurotic patients show the most severe and prolonged psychophysiological reactions. Among the reactions seen in the hysterical group are vaginismus, globus hystericus and various skin disorders. Atopic dermatitis, in particular, is more severe and prolonged in hysterical than in obsessive-compulsive patients. The mechanism of hysterical autonomic disturbances explains the apparent contradition, if one bears in mind that sensorimotor cortex contains one of the three important cortical autonomic integrating centers, and that a focal inhibition there as part of a milder neurosis such as a conversion reaction can produce a greater degree of release of "regressive innervations" to skin than can a severe but more diffuse kind of cortical inhibition.

Psychophysiological reactions occur whenever stress evokes the inhibitory overactivity of the anxiety mechanism to the degree and extent necessary to release the autonomic centers of the hy-

pothalamus from cortical integration in keeping with present needs. Earlier, "schizokinetic" patterns then emerge. Szasz has termed these "regressive innervations." Adaptive as they must have been at one time in the life of the individual, they now occur simply as a consequence of the diffuse inhibition which anxiety produces in the cerebral cortex. Naturally specificity does not exist in any clear and universal way and formulations which give this impression may be accurate descriptions of some patients but they cannot be regarded as valid mechanisms in the light of present knowledge. Grinker stresses the fact that each case involving psychophysiological disturbances must be studied in terms of the way in which the individual has experienced stresses and how he has become conditioned to react to them throughout life. To do this in a general practice setting the physician needs only his medical common sense plus some specific knowledge about the physiology of emotions and anxiety.

BOOK REVIEWS

ROENTGEN SIGNS IN CLINICAL DIAGNOSIS by Isadore Meschan, M.A. M.D. 1st Edition. 1058 pages with 2216 illustrations on 780 figures. Philadelphia: W. B. Saunders Company, 1956. $20.00.

This text is written for medical students, residents in radiology and allied specialties, and practicing physicians.

The author presents the fundamentals of radiology rearranged on the basis of objective signs as seen in roentgenograms. The text is organized to reveal the limitations as well as accuracy in roentgen diagnosis by pointing to the technical and anatomical facets behind roentgen signs. It encourages the reader to systematic thinking and analysis of roentgen signs prior to the formation of definitive diagnosis, thus largely eliminating the need to know or strongly suspect the patient's disease before one can evaluate the patient's X-ray film.

Representative X-ray films of disease structures are identified. The author with the aid of clear, distinct line drawings, explains the structural changes that account for altered radiographic appearances. Radiologic studies of the entire body by areas are covered. The author shows why the image appears as it does and explains structural changes accounting for altered radiographic appearance.

L.D.

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CLINICAL PATHOLOGY, APPLICATION AND INTERPRETATION by Benjamin B. Wells, M.D., Ph.D., Cloth. Second Edition. 488 pages. Philadelphia: W. B. Saunders Company, 1956.

This book written for medical students and physicians has a refreshing approach. It is divided into ten chapters, covering such broad topics as Infectious Diseases, Diseases of Blood, Metabolic Diseases and Diseases of the Gastrointestinal System.

The author briefly discusses the physiology and clinical picture of each group of diseases. He then discusses the laboratory tests used in help making the diagnosis, including the rational for the test. Furthermore, there is mention of what other diseases can give similar values. For example, these is a differential diagnosis of *neutropenia*. He also approaches the subject, for example, of what tests to order in making a diagnosis of the etiology of *coma*.

One of the fine points of the book is that the actual mechanics of the tests are reserved for the last chapter.

This book reads much like a novel and is highly recommended.

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DERMATOLOGY by Donald M. Pillsbury, M.A., D.Sc. (Hon.), M.D., Walter B. Shelly M.D., Ph.D., Albert M. Kligman, M.D., Ph.D. 1331 pages, 564 figures. Philadelphia-London: W. B. Saunders Company, 1956. $20.00.

All the major criteria for a good textbook are present in abundance in this new volume on dermatology. The anatomy, embryology, and physiology of the skin and its appendages are fully covered, and are followed by a comprehensive review of the pathological diseases of the skin. Both sections are carefully illustrated by diagrams and photographs.

The authors endeavor to impress the reader with a systematic method of diagnosing and treating disorders of the skin. A method of outlook, rather than a list of diseases, orientates the reader to the general classifications into which skin diseases fall. The different conditions are discussed as effecting different parts of the organ; thus, diseases of the apocrine glands, diseases of the blood vessels, disturbances of pigmentation, diseases of the hair, etc. The diseases affecting the skin as a whole are in separate chapters; as: metabolic and nutritional diseases, viral and rickettseal infections, dermatological parisitology, and hereditary cutaneous disorders.

Special sections are given over to the discussion of therapeutics. Among these, the review of X-ray radiation and surgical diathermy were very intelligently written, and are considered from an unbiased level. The chapter on the use of corticosteroid therapy is one I would earnestly recommend, it is a sober appraisal of these new agents, is very up to date and contains a list of those conditions which the authors have clinical evidence on a large number of cases.

Cognizance of the researches of psychosomatic medicine is taken with exemplary restraint in a chapter that psychiatrists and dermatologists will both subscribe to. The authors ignore the extremists in both specialties, and present a clear description of those deramtological disorders that are proven to have a psychiatric etiology.

This book is almost encyclopedic in its completeness, it is well organized and well written. Both the student and the practicing physician will find this a valuable book.

B.H.R.

ABSTRACTS SECTION

FOA, PIERO P. *(Dept. of Physiology and Pharmacology).* The Control of the Secretory Activity of the Islets of Langerhans. Ciba Foundation Colloquia on Endocrinology. *9*:55, 1956.

Insulin secretion appears to be influenced to a small extent by nervous stimuli originating in the brain stem and, to a greater extent, by the concentration of glucose and, possibly of galactose in the blood. In addition, B cell activity seems to be under the influence of STH, ACTH, sex hormones, glucagon and of insulin, itself. A brief review of these relationships introduces a discussion of the effects of prolactin.

The first injection of prolactin into normal dogs causes hypoglycemia associated with profound degranulation of the beta cells and with the liberation of insulin into the blood of the pancreatic vein. Subsequent injections cause hyperglycemia. Examination of the pancreas at this time reveals that, although some restoration of the beta granules has occurred, the recovery is not complete. This suggests that prolactin may exert its so-called diabetogenic effect through a "stimulation-exhaustion" mechanism, in a manner similar to that of other pituitary hormones. Prolactin hyperglycemia is not accompanied by the liberation of glucagon and occurs also in the depancreatized dog. For this reason, it is postulated that prolactin, like STH, may inhibit the utilization of glucose by the tissues.

Glucagon secretion appears to be regulated mainly by the concentration of blood glucose and by anterior pituitary STH. The intravenous injection of STH causes hyperglycemia accompanied by the appearance of hyperglycemic material in the blood of the pancreatic vein. This, however, is a controversial point, and the opposing points of view are discussed.

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BLIVAISS, B. B., Ph.D., HANSON, R. O. Ph.D. (by invitation), KUTUZOV, H., M.S. (by invitation), and PESCHIN, A., B.S. (by invitation, *Dept. of Physiology and Pharmacology).* Effects of Anti-ICSH Serum on Testes of Estrogen-Treated Strain A Mice.* The Chicago Medical School.

Sheep pituitary ICSH was prepared by the method of Li (Endrocinology 28:803, 1940). On assay in hypophysectomized male rats, 0.06 Gm. of ICSH (dried gland equivalent) induced a 100 per cent increase in ventral prostate weight. Anti-ICSH serum prepared by injection of ICSH into rabbits was assayed in immature male rats (method of Deutsch, Am. J. Physiol. 162:393, 1940). Response of the ventral prostate to ICSH was reduced 15 per cent with 0.125 ml. of antiserum. After five months pretreatment with 0.02 mg. of estradiol benzoate weekly, 159 strain A mice were continued on estradiol but divided into the following daily treatment groups: 1) 0.2 ml. of anti-serum or 2) normal serum; 3) 0.025 Gm. (dried gland equivalent) of ICSH; 4) continued on estradiol. After one week, testes weights were significantly reduced in the antiserum group and at five weeks weighed 25 per cent of the estradiol controls. Seminal vesicle weights were reduced by the third week. The normal serum group showed little deviation from the controls. For four weeks the ICSH group showed a gradual increase in weights of testes and seminal vesicles. Thereafter, the weights declined as treatment continued. Histologic examination of samples from the 4 groups suggests that the reductions in testes weights were due primarily to decrease in size and number of the Leydig cells.

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BLIVAISS, BEN B., Ph.D., HANSON, R. O., Ph. D., ROSENZWEIG, R. E., B.S., and KUTZOV, H., M.S. *Dept. of Physiology and Pharmacology).* Effect of Progesterone on the Induction of Leydig Cell Tumors with Estrogen in Strain A Mice. The Chicago Medical School, Chicago 12, Illinois.

Gardner (Anat. Rec. *68*:339, 1937) postulated that estrogens elicit an increased production of pituitary interstitial-cell-stimulating hormone (ICSH) which is responsible for production of testicular interstitial-cell tumors. Since progesterone is known to have an inhibitory effect on production and/or release of LH or ICSH, a comparison was made of the effect of separate and combined injections of diethylstilbestrol (DES) and progesterone (P) on development of interstitial ial cell tumors. A group of 175 strain A mice, 4-5 weeks old, were divided into the following treatment categories: (1) .05-0.25 mg DES per week, (2) 1.25 mg P weekly, (3) combination of DES and P as above, and (4) 0.05 cc sesame oil weekly.

Of 55 DES-treated mice autopsied after 4 months of age, when the first tumor appeared, 76% had tumors of which 5 cases were unilateral and 37 were bilateral. After 9 months of age, all mice had bilateral tumors. Of 45 DES-and P-treated cases autopsied after 4 months of age, 45% had tumors, of which 9 cases were unilateral and 14 were bilateral. First tumor was not found until 7 months of age. Mice receiving progesterone only showed an underdevelopment of interstitial cells both as to number and size up to 6 months of age, but thereafter attained normal development.

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FOA, P. P., COSTA, E., GALANSINO, G., and POZZA, G.: Glycogen Stores in Glucagon-Treated Rats. II Effect of Alloxan Diabetes. Proc. Soc. Exp. Biol. and Med., *91*:574, 1956.

The effects of glucagon and of epinephrine on liver and muscle glycogen and adrenal ascorbic acid of alloxan diabetic rats were studied. Twenty minutes after the injection of epinephrine a decrease in liver and muscle glycogen was observed. The decrease was still greater after two hours. Two hours after injection of glucagon there was a decrease in liver glycogen and, in one experiment, an increase in muscle glycogen. Twenty-four hours after the injection of glucagon, liver glycogen had returned to, but not above, the initial level. The adrenal glands of alloxan diabetic rats are significantly larger than those of normal rats. The injection of glucagon or epinephrine may further stimulate the adrenal cortices, as indicated by an occasional decrease in their acsorbic acid content.

It is concluded that: a) the glycogenolytic effects of glucagon and epinephrine are unimpaired in alloxan diabetes, and b) the delayed increase in liver glycogen, observed in normal rats after the injection of epinephrine or glucagon, requires the presence of an intact insulin-secreting system capable of being stimulated by epinphrine or glucagon hyperglycemia.

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COSTA, E., GALANSINO, G., and FOA, P. P. *(The Chicago Medical School, Chicago).* Glycogen Stores in Glucagon-Treated Rats. I. Time Factors. Proc. Soc. Exp. Biol. and Med., *91*:308, 1956.

The effects of glucagon and epinephrine on muscle and liver glycogen and on adrenal ascorbic acid were studied in two hundred thirty-one adult Sprague-Dawley ablino rats. The results show that twenty minutes after injection of epinephrine there was a decrease in liver and muscle glycogen and in adrenal ascorbic acid. Two hours after the injection, liver glycogen was significantly higher than in controls, while muscle glycogen and adrenal ascorbic acid were still below normal. Glucagon caused immediate decrease in liver glycogen. When large doses were used this decrease was followed twenty-four hours later by secondary increase to values greater than normal. Glucagon caused an occasional slight increase of muscle glycogen.

It is suggested that the primary effect of epinephrine and of glucagon in all doses is an acceleration of liver glycogenolysis and that their glycostatic effects are due to secondary increases in secretion of insulin and/or adrenal cortical hormones.

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POZZA, GUIDO (by invitation), GALANSINO, GIORGIO (by invitation), and FOA, PIERO P. *Dept. of Physilogoy and Pharmacology),* The Chicago Medical School. Insulin Secretion Following N—(n-butylcarbmyl) Sulfanilamide (BZ-55) Injections. Sept. Meeting Amer. Physiol. Society, Rochester, N.Y.

Purpose of this work was to investigate the possibility that N,—(n-butyl-carbamyl sulfanilamide (BZ-55) may cause hypoglycemia by stimulating insulin secretion. Pancreatic-femoral and mesenterio-femoral cross-circulation experiments were performed using normal dogs anesthetized with Nembutal and heparinized.

After a control period, BZ-55 (50 mg/kg) was injected I.V. into the donor *Dog D.* The concentration of glucose and BZ-55 in the blood of *Dog D* and of the recipient *Dog R* was determined at intervals for 3 to 4 hours. The results indicate that the injection of the drug is followed by a decrease in blood glucose of approximately 30% in *Dog D,* accompanied by a still greater decrease in *Dog R.* The concentration of BZ-55 reached a maximum of 100 mg/1 in the blood of *Dog D* and of 15 mg/1 in the blood of *Dog R.*

When *Dog R* received mesenteric instead of pancreatic blood from *Dog D,* its blood sugar did not decrease, although the concentration of BZ-55 in its blood also reached values of about 15 mg/1. The results suggest that BZ-55 stimulates the pancreas causing an immediate release of insulin. The possible harmful effects of a continued stimulation of the Islets of Langerhans in animals and man with decreased pancreatic reserve must be investigated before BZ-55 can be recommended for the treatment of diabetes mellitus. (Aided by grant A-522, NIH).

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